A STUDY ON CARCINOMA TONGUE

DISSERTATION SUBMITTED FOR

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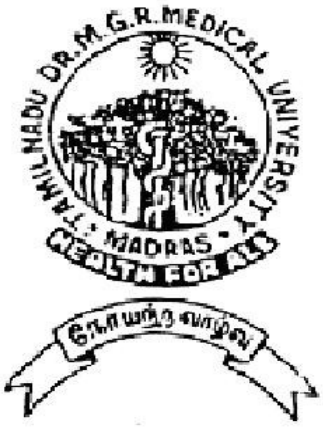

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled " A STUDY ON CARCINOMA TONGUE " is bonafide record work done by Dr. VASANTHA KUMAR.G under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.S branch I (General Surgery)

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I, **Dr. VASANTHA KUMAR.G** solemnly declare that this dissertation titled **"A STUDY ON CARCINOMA TONGUE"** has been done by me from June 2006 to April 2008. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University Board either in India or abroad.

This is submitted to The Tamil Nadu Dr.M.G.R.Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Master of Surgery degree Branch-I (General Surgery) to be held in March 2009.

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CONTENTS

INTRODUCTION

The tongue is a vital structure essential for initiating the first phase of swallowing, moving food in the oral cavity to permit adequate mastication, to enjoy the taste of delicious food and of course for articulation. In toto it makes the life lively and lovely. Therefore it is no wonder that any abnormality of the tongue will cause the patient significant dysfunction.

In India, cancer of the tongue occurs in approximately 30,000 people in a year nearly 7500 persons die of carcinoma tongue.

Early detection is the key to an effective cure of carcinoma tongue with minimal disability.

Unfortunately in our part of the world the people are more prone to develop oral cancers because of tobacco habituation in various forms, and also report for treatment at advanced stage because of various reasons.

AIM OF THE STUDY

1. To study the various anatomical site wise distribution of carcionoma tongue in southern Tamil Nadu.

2. To study about various predisposing factors, age, sex distribution of carcinoma of the tongue.

3. To compare the merits and demerits of various modalities of treatment like surgery, radiotherapy and chemotherapy in combination or alone.

4. To evaluate the guide lines for the future management of carcionoma of the tongue and to give the maximum benefit to the suffering patients.

SURGICAL ANATOMY OF TONGUE

The tongue is a highly muscular organ of deglutition, taste and speech. Partly oral and partly pharyngeal in position and is attached by its muscles to the hyoid bone, mandible, styloid process, soft palate and the pharyngeal wall.

It has a root, apex, a curved dorsum and an inferior surface. Mucosa is normally pink, moist, and attached closely to the underlying muscles. The root of the tongue is attached to the hyoid bone and mandible. Dorsum is divided by V shaped sulcus terminalis into an anterior, oral or presulcal part which is facing upwards and Posterior, pharyngeal or postsulcal part facing posteriorly which forms posterior 1/3 of the tongue.

The two limits of sulcus terminalis run anterolaterally to the palatoglossal arches from a median depression called foramen ceacum which is the site of upper end of the embryonic thyroid diverticulum.

TONGUE – ORAL PART:

Located in the floor of the oral cavity, has an apex touching the incisior teeth, a margin in contact with the gums and teeth. Superior surface

is related to hard and soft palates. Dorsal mucosa has a longitudinal median and is papillated.

The inferior mucosa is smooth, purplish and reflected on to the oral floor and gums, which is being connected to the former anteriorly by the median muscular fold – frenulum linguae. Lateral to this on either side deep lingual veins are visible. Lateral to the veins is a fringed mucosal ridge called as plica fimbriata.

PHARYNGEAL PART:

Forming the base of the tongue lies posterior to the palatoglossal arches within oropharynx. Its mucosa is reflected laterally on to the palatine tonsils and pharyngeal wall and posteriorly on to the epiglottic folds. Devoid of papillae it has low elevations due to lymphatic nodules embedded in the submucosa, which are collectively called as lingual tonsil. The ducts of small seromucous glands open on the apices of these elevations.

DEVELOPMENT OF TONGUE:

Anterior 2/3 of the tongue develops from the lingual swellings of the mandibular arch and form the tuberculum impar. Posterior 1/3 of the tongue develops from the hypobranchial eminence.

LINGUAL PAPILLAE:

These are projections of mucosa from the dorsum of the tongue which are limited to anterior 2/3 of the tongue. There are 4 types. These projections are modifications of mucous membrane which increase the area of contact between the tongue and the contents of the mouth. The four types are

1.filiform papillae

2. fungiform papillae

3. vallate papillae

4. others.

LINGUAL MUSCULATURE:

Tongue is divided by a median fibrous septum attached to the hyoid bone. In each half are both the extrinsic and intrinsic muscles.

Extrinsic muscles:

Genioglossus: triangular in sagittal section, linear and parallel to the midline, arises from superior genial tubercle behind the mandibular symphysis. From this point its fans out backwards and upwards. Inferior fibres of genioglossus are attached by a thin aponeurosis to the upper anterior surface of the hyoid body near the midline. Muscles of opposite

sides are separated posteriorly by the lingual septum. Genioglossus brings about forward traction of the tongue and acting bilaterally, the two muscles depress the central part of the tongue, acting unilaterally the tongue diverges to the opposite side. The nerve supply is hypoglossal nerve.

Hyoglossus: Thin, quadrilateral muscle attached to the whole length of the greater cornu and the front of the body of the hyoid bone. Passing almost between styloglossus laterally and the inferior longitudinal muscle medially. Hyoglossus depresses the tongue and is supplied by hypoglossal nerve.

Chondroglossus: This is described as a part of hyoglossus. 2cm in length arises from the medial side and base of the lesser cornu and the adjoining part of the hyoid body and ascending to merge with theinrinsic musculature between the hyoglossus and genioglossus. The action is to assist the hyoglossus to depress the tongue.

Styloglossus: Shortest and smallest of the three styloid muscles. It arises from the anterolateral aspect of the styloid process near its apex amd from the down and forwards, it divides at the side of the tongue in to a longitudinal part which enters the tongue dorsolaterally and an oblique part overlapping the hyoglossus and decussating with it. The action is to draw the tongue up and backwards and is supplied by hyoglossus nerve.

Palatoglossus: Arises from the palatine aponeurosis of the soft palate inserted to the side of the tongue at the junction of the anterior 2/3rd and posterior 1/3rd, elevates the tongue and opposes it with the soft palate. The nerve supply is cranial accessory.

INTRINSIC MUSCLES:

Superior longitudinal muscle: extends forwards from the submucous fibrous tissue near the epiglottis and from the median lingual septum into the lingual margins. Some fibres being inserted into the mucous membrane.

Inferior longitudinal muscle: Close to the inferior lingual surface between genioglossus and hyoglossus. Extends from the lingual root to the apex. Some of its posterior fibres being connected to the body of the bone and anteriorly blends with styloglossus.

Transverse muscles: Passes laterally from the median fibrous septum to the submucous fibrous tissue at the lingual margin blending with palatopharyngeus.

Vertical Muscles: Extend from the dorsal to the ventral aspects of the tongue in the borders of its anterior part. All the intrinsic muscles are supplied by hypoglossal nerve.

Intrinsic muscles of the tongue alter the shape of the tongue. The superior and inferior longitudinal muscles shorten the tongue. The former

also turn the apex and sides upwards to make the dorsum concave, later pulls the apex down to make the dorsum convex.

Transverse muscle narrows and elongates the tongue. Vertical muscle makes it flatter and wider. Acting alone or in pairs and in endless combination they give the tongue precise and highly variable mobility. Important not only in alimentary function but also in speech.

LINGUAL GLANDS:

Three types: Mucous, serous and mixed types. Mucous glands are like the labial and buccal glands in structure. They are numerous in the post sulcal region, and also present at the apex and margins.

TASTE BUDS:

Taste buds are little barrel shaped pale staining structures arranged at right angles to the surface of the mucous membrane of the mouth and the throat. They present plenty on the dorsum of the tongue particularly along the sides of the groove that surround the vallate papillae and epithelium between the paplillae. A taste bud is spindle shaped and has a layered appearance like an onion under the microscope.

Two kinds of cells called sustencular cells and neuroepithelial taste cells are present. Sustencular cells are narrower at their ends and they pursue a curved course from one end of the bud to the other. The end of the bud

reaches the surface and there are cells which are arranged so as to surround a little pit that opens on the surface through fine inner taste pores.

The neuroepithelial cells which are long narrow cells are intermingled with sustencular cells in the more central part of the bud. The free ends of these cells extend into the pits at the end of taste bud. They give rise to short hairs that extend into the pit.

Any substance to be tasted gets dissolved in saliva and passes by means of a pore into the pit of the taste bud where it stimulates the hairs of the neuroepithelial cells setting up a nerve impulse. There are basic tastes like sweet, sour, salty, bitter and perhaps alkaline and metallic.

NERVE SUPPLY OF THE TONGUE:

SENSORY NERVES:

Lingual branch of mandibular nerve is for general sensation of the anterior 2/3rd of tongue. Chorda tympani branch of the facial nerve running in the sheath of lingual nerve for gustation in the anterior 2/3rd region exclusive of vallate papillae.

Lingual branch of the glossopharyngeal nerve distributed to the posterior 1/3rd mucosa, lateral aspect and to the vallate papillae. It mediates general and gustatory sensation. Superior laryngeal nerve sends fine branches to the root immediately infront of the epiglottis.

MOTOR INNERVATION:

Motor supply to all lingual muscles except palatoglossus is through hypoglossal nerve. Palatoglossus is supplied by pharyngeal plexus.

Parasympathetic supply:

Parasympathetic supply of the various glands of the tongue is from chorda tymphani which is a branch of facial nerve. It get synapsed in the submandibular ganglion and then distributed to the tongue mucosa via the lingual branches.

Sympathetic supply:

Sympathetic supply to lingual glands and vessels enters in tongue through the plexus around its arteries arising from carotid plexus. In posterior 1/3rd of the tongue isolated nerve cells have been observed perhaps post ganglionic parasympathetic neurons probably innervating glandular tissue and vascular smooth muscles.

ARTERIAL SUPPLY:

Main arterial supply is through lingual branch of the external carotid artery. Tonsillar, ascending palatine branches of the facial and ascending pharyngeal arteries also supply the lingual root.

In the vallecula, epiglottic branches of the superior laryngeal artery get anastamosis with the inferior dorsal branches of the lingual artery.

Lingual muscles are supplied by this rich anastamotic network and there is a very dense submucosal plexus.

VENOUS SUPPLY:

Dorsal lingual veins drain the dorsum and sides of the tongue and join the lingual veins which accompany the lingual artery between hyoglossus and genioglossus. Near the greater cornu of the hyoid bone, they join the internal jugular vein. Deep lingual veins drain the tip of the tongue. Near the anterior border of hyoglossus it joins a sublingual vein.

LYMPHATIC DRAINAGE:

Lymphatic plexus in the lingual mucosa is continuous with an intramuscular plexus. The anterior lingual region drains into the marginal and central vessels and behind the vallate papillae into the dorsal lymph vessels. Vessels are divided into marginal, central and dorsal vessels.

Marginal Vessels:

They come from lingual apex and frenular region and descend under the mucosa to widely distributed nodes. Some vessels pierce the mylohyoid in contact with mandibular periosteum to enter the submental nodes and also pass anterior to the hyoid bone to jugulo-omohyoid node. Vessels arising in the plexus on one side may cross under the frenulum to end in the contralateral nodes. Efferent vessels of submental nodes which are median,

pass to both sides. Some vessels pierce the mylohyoid to enter anterior or middle submandibular nodes. Some pass inferior to the sublingual gland and accompany the companion vein of the hypoglossal nerve and in jugulo-digastric nodes. One often descent further superficial or deep to the intermediate tendon of the diagastric to reach the jugulo-omohyoid node. Some vessels from the lateral margin cross the sublingual gland pierce the mylohyoid and end in the submandibular nodes. Others end in jugulo-digastric or jugulo-omohyoid nodes. Vessels from the posterior part of the lingual margin traverse the pharyngeal wall to the jugulo-digastric lymph nodes.

Central Vessels:

The regions of the lingual surface draining into the marginal or central vessels are not distinct. Central vessels descend between the genioglossi, some turning laterally through the muscles, but most pass between them and diverge to the right or left following the lingual veins to the deep cervical nodes especially the jugulo-digastric and jugulo-omohyoid. Some pierce the mylohyoid to enter the submandibular nodes.

Dorsal Vessels:

Draining the region of the vallate papillae and behind them run postero-inferiorly. Some near the median plane to both sides. They run laterally to join the marginal vessels, all pierce the pharyngeal wall, passing around the external carotid arteries to reach the jugulo-digastric and jugulo-omohyoid nodes. One may descend posterior to the hyoid bone, perforating the thyrohyoid membrane to end in the jugulo-omohyoid node.

Significant feature of the lymphatic drainage of the tongue, which is through the floor of the mouth, is that from one side especially of the posterior part may reach nodes of both sides of the neck. This contralateral flow usually only occurs when the ipsilateral channels have been obstructed.

RISK FACTORS FOR THE DEVELOPMENT OF CARCINOMA OF THE TONGUE

The risk factors are

1. Tobacco
2. Alcohol
3. Chronic irritation due to sharp teeth etc.,
4. Vitamin deficiencies

TOBACCO:

Tobacco appears to be a risk factor for most cancers originating in the tongue. Relative risk of cancer of the tongue increases with increasing amount and duration of tobacco use. Wynder and stellman estimated a relative risk for 4.8 for men who smoked 1-5 cigarettes per day and 8.1 for those who smoked 10 or more cigarettes per day, when compared with non smokers. Tobacco appears to act as an initiator as well as promoter and the relative risk decreased after cessation of smoking.

ALCOHOL:

Alcohol has been implicated as a risk factor for oral, pharyngeal and laryngeal cancers. Overall risk of cancer of the oral cavity and pharynx was

found to be positively associated with the amount of any type of alcohol consumed (beer, wine or hard liquor). William and Horn reported the highest relative risks for oral cavity and larynx cancer among male beer drinkers and for pharyngeal cancer among wine drinkers. Liber et al reviewed possible mechanisms by which alcohol abuse or related disease may initiate the development of cancer.

1. Local effect due to direct contact: direct contact with susceptible tissues may increase the risk of cancer through carcinogens in the consumers of alcohol.

2. Presence of carcinogens: Some of the containments in alcohol beverages are Polycyclic hydrocarbons, fuel oil and nitrosoamines which are carcinogens.

3. Cellular injury produced by ethanol and its metabolite acetaldehyde affect target tissues. After chronic ethanol consumption hepatic mitochondria become more susceptible to the toxic effects of acetaldehyde. Although mutagenicity of ethanol has not been demonstrated, acetaldehyde has been found to be mutagenic for human lymphocytes.

4. Nutritional deficiencies: Alcoholics have nutritional deficiencies which has been associated with development of malignancies.

CHRONIC IRRITATION:

Trauma and local irritation are considered extremely important in the etiology of carcinoma tongue. Malocclusion producing chronic cheek bite, ill fitting dentures, sharp teeth which constantly irritate the mucosa.

Hot spicy foods are also to be considered as risk factors.

Poor oral and dental hygiene are also one of the predisposing factors.

VITAMIN DEFICIENCIES:

It is well recognized that a deficiency of vitamin A will induce metaplasia and keratinization of certain epithelial structures, particularly of the glands of the respiratory mucosa. Vitamin B complex deficiency has also been suggested as a predisposing factor which must be related to the alteration in the oxidation patterns of the epithelium.

PREMALIGNANT LESIONS

A premalignant lesion is a morphologically altered tissue in which malignancy is more likely to occur.

The premalignant lesions are

1. Leukoplakia
2. Erythroplakia
3. Submucous fibrosis
4. Carcinoma in situ

LEUKOPLAKIA:

It is a white plaque on the oral mucous membrane produced by several conditions including epidermal proliferations like tobacco, chronic cheek bite, lichen planus, palatitis nicotina and candidiasis. By definition Leukoplakia is a white plaque on the oral mucous membrane that cannot be

removed by scraping and cannot be classified clinically and microscopically as another disease entity.

ERYTHROPLAKIA:

Red, velvety, possibly eroded area with in the oral cavity that usually remains level with or may be slightly depressed in relation to the surrounding mucosa. The epithelial changes in such lesions tend to be markedly atypical, incurring a much higher risk of malignant transformation (18-20%) than that of leukoplakia (5-9%)

SPECKLED LEUKOERYTHROPLAKIA:

Occasionally intermediate forms are encountered that have the characteristics of both leukoplakia and erythroplakia. They appear as solitary/multiple white patches or plaques with indistinct/sharply demarcated borders. They may be slightly thickened, smooth, wrinkled, indurated or may appear as raised. Sometimes they are corrugated or verrucous plaques. Histologically they present as an epithelial spectrum ranging from hyperkeratosis overlying a thickened, acanthotic but orderly placed mucosal epithelial lesions with markedly dysplastic changes. Sometimes they are merged with carcinoma in situ.

SUBMUCOUS FIBROSIS:

It is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although preceded occasionally by vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic change of lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.

It may be related to a particular dietary component like chillie. Histology shows atrophy of oral epithelium with complete loss of rete pegs. Underlying connective tissue shows severe hyalinization with homogenization of collagen bundles.

SQUAMOUS CELL CARCINOMA:

More than 95% of the Malignancy of tongue are squamous cell carcinoma 2% of all cancer deaths in male, 1% of all cancer death in female are due to squamous cell carcinoma tongue. In early stages malignancy appear either as raised, firm, plaques or as irregular, roughened or verrucous area of mucosal thickening possibly mistaken for leukoplakia. Either pattern may be superimposed on a background of apparent leukoplakia or erythroplakia. As these lesions enlarge they create, protruding masses and undergo central necrosis forming an irregular, shaggy ulcer rimmed by

elevated, firm, rolled border. Squamous cell carcinomas of the oral cavity take months to years to progress from carcinoma in situ often being preceded by leukoplakia to invasive cancer and so every death they cause must be viewed as a preventable tragedy.

THE ROLE OF SURGICAL PATHOLOGY IN DIAGNOSIS AND MANAGEMENT

Surgical biopsy:

The simplest and most commonly utilized method is 'Punch biopsy'. Histological diagnosis is straight forward mostly. Exophytic lesions which are highly differentiated at the surface, i.e., verrucous carcinoma may not yield tissue, truly representative of the growth. Ulcerative lesions which are post irradiation recurrence may be difficult to punch. For these cases 'wedge biopsy' or incision biopsy has to be taken.

Fine Needle Aspiration Cytology:

It is an excellent technique for confirming metastatic disease in enlarged lymph nodes. Sometimes micrometastasis may be missed due to sampling error. Accuracy is about 40%.

Frozen section Biopsy:

Mostly used intraoperatively to determine the status of cervical lymph nodes and excision margin. Frozen section are used for primary diagnosis of squamous cell carcionoma of the tongue.

Tumour thickness and depth of invasion:

The depth of invasion is the portion of tumour below the plane of normal surrounding mucosa. Tumour thickness correlates well with survival.

PATHOLOGICAL CLASSIFICATION OF CARCINOMA TONGUE:

1. Squamous cell carcinoma.
2. Tumour arising from minor salivary glands.
    - Adenoid cystic carcinoma
    - Mucoepidermoid carcinoma

- Lymphoma.

3. Soft tissue sarcoma
4. Mucosal melanoma
5. Plasmacytoma

AJCC – STAGING OF ORAL CANCERS

T_x - Primary tumour cannot be assessed

T_o - No evidence of primary tumour.

T_{is} - Carcinoma in situ.

T_1 - Tumour 2cm or less in greatest dimension.

T_2 - Tumour more than 2 cm but not more than 4cm in greatest dimension.

T_3 - Tumour more than 4cm in greatest dimension.

T_4 - Tumour invades adjacent structures.

T_{4a} - Tumour involving cortical bone, deep (extinsic) muscle of tongue, maxillary sinus and floor of the mouth.

T_{4b} - Tumour invades masticator space, pterygoid plates of skull base.

STAGING OF CERVICAL LYMPH NODES

N_x - Regional nodes cannot be assessed.

N_o - No Regional lymph node metastasis.

N_1 - Metastasis in single ipsilateral lymph node 3 cm or less in greatest dimensions.

N_{2a} - Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6cm in greatest dimension.

N_{2b} - Metastasis in multilple ispilateral lymph node, none is more than 6cm in greatest dimension.

N_{2c} - Metastasis in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension.

N_3 - Metastasis in a lymph node more than 6cm in greatest dimension.

DISTANT METASTASIS

Mx - Presence of distant metastasis can not be assessed.

Mo - No distant metastasis

M1 - Distant metastasis

STAGING

STAGE I - $T_1N_0M_0$

STAGE II - $T_2N_0M_0$

STAGE III - $T_3N_0M_0T_{1,2,3}N_1,M_0$

STAGE IV - $T_4N_0M_0$, $T_{1,2,3,4}$ $N_{2,3}M_0$ any T, and N, M_1

LEVELS OF NECK NODES

Level-Ia: Nodes in submental triangle.

Ib: Nodes in Submandibular triangle

Level-II: Jugular nodes extending from the subdigastric area down to the carotoid bifurcation and the nodes surrounding the spinal accessory nerve from jugular foramen to the posterior border of sternomastoid. Includes nodes in the upper posterior cervical triangle above the entrance of the spinal accessory nerve in to this triangle.

Level III: Nodes along the middle 1/3 of the internal jugular vein-between the cartoid and its bifurcation to the posterior border of the sternomastoid and the omo hyoid muscle or cricothyroid membrance.

Level IV: Nodes along the lower 1/3 of the internal jugular vein between the omohyoid muscle above, the clavicle below, behind the carotid vessels and anterior to the omohyoid muscle.

Level V: Nodes in the posterior triangle – Borders are formed by posterior edge of the sternocleido mastoid muscle, the level of the entrance

of the spinal accessory nerve, the trapezius muscle, the posterior belly of the omohyoid muscle.

Level VI: Pretracheal, paratracheal and anterior cervical node group.

APPROACH TO THE CARCINOMA TONGUE PATIENTS

The comprehensive care of carcinoma of the tongue patients begin with pretreatment consideration that include the assessment of the general medical condition, nutritional status, dental and oral hygiene, and appropriate choice of medical therapies that designed to minimise the treatment related complication. Confirmation of the diagnosis by tissue biopsy, the nodal secondaries mostly confirmed by FNAC. To rule out lung and liver metastasis we have to do X-ray chest and ultrasonogram Abdomen studies.

Common microbials isolated from infected wounds include both aerobes and anaerobes with Bacteroids fragilis, E.coli, β Hemolytic streptococci, staphylococcus, pseudomonas. Perioperative antibiotics should continue for 72 hours post operatively depending on the likely hood of infection. Antibiotics regimen should allow for broad spectrum coverage.

Antibiotics should include sulbactum and ampicillin or Metronidazole combined with cephalosporins.

LITERATURE REVIEW OF VARIOUS MODALITIES OF TREATMENT

General Principles of surgery in carcinoma of the tongue:

In the delivery of effective surgical management, the single most significant principle is the adequate preoperative assessment of the disease extent. Adequate surgical clearance has to be given to the diseased site. For surgery, electrocautery dissection, Laser ablation and Harmonic scalped can be utilized. Recent development in the management of cervical lymph node disease involve more conservative surgical procedure. In those patients who are not likely to receive careful post operative follow up, it is recommended that elective radical neck dissection can be performed.

General principles of Radiation therapy:

For early state disease both radiation and surgery are frequently curative and can produce similar rates of cure. Selection of treatment can be individualized to each patient and must consider issues like cosmetic and functional outcome, quality of life, speed with which treatment can be completed, patient, reliability, risk of subsequent cancers etc., If surgery is planned, there is no indication for pre-operative radiotherapy. Definitive surgery should be performed and post operative radiotherapy can be used. In planning treatment for advanced lesions it is essential to separately consider the primary site and the metastatic neck. Adequate dose of well delivered post operative radiotherapy can sterilize cancer positive surgical margins. Side effects of radiotherapy are classified into acute and late complications. Acute effects generally related to inflammatory reactions in the tissues within the radiation field like epidermitis, mucositis, loss of taste. Irradiation of salivary glands cause dryness of mouth. Irradiation of lacrimal glands can cause dryness of the eyes.

Any dental works should be done prior to the initiation of radiation. Patient should be placed on dental prophylaxis with fluoride application. It has also been clearly shown that dental extraction in an irradiated mandible can lead on to osteonecrosis.

Combined external beam irradiation plus brachytherapy is commonly employed for cancers of the tongue. This allows very high doses to the tumour with implant which also serves to minimise radiation to the surrounding normal tissue. This will serve to increase the local control as well as to improve the functional and quality of life outcome. Brachytherapy alone can be used for early lesion of the tongue and external RT to be held in reserve for potential future use.

External radiotherapy is usually delivered once a day. 5 days per week, continuous course until the desired dose is achieved. In general 50-60 cGY in 5-6 weeks. Because the anatomic separation in the head and neck region is thinner than other parts of the body, a low energy linear accelerator is preferred.

General Principles of Chemotherapy:

Neo Adjuvant Chemotherapy: Given before ablative surgery or radiotherapy, the main advantage is preservation of the organ function, Neoadjuvant chemotherapy eliminates the pharmocologic sanctuary problems that is poor vascularity leading to the poor concentration of chemotherapy after surgery or radiotherapy. Initial chemotherapy result is increased compliance, responsiveness and tolerance of higher dosage. Down staging of the primary and regional node disease has successfully allowed

for organ preservation and reduction in distant micrometastasis. Cisplatin and 5FU combination remains the most active regimen.

Post Operative adjuvant chemotherapy:

Chemotherapy administered after the patient has been rendered disease free with surgery or radiotherapy. The rationale behind that, are, for resectable disease definitive surgery is not delayed. When neo adjuvant chemotherapy is successful, tumour margins are blurred and the extent of the required surgery may be uncertain, in trials of neo adjuvant chemotherapy up to 20% of patients refused surgery once response was achieved and their symptoms abated.

There was a significant increase in time to develop distant metastasis for patients receiving adjuvant chemotherapy. The overall comparison shows there is no significant difference in overall survival, disease free survival or time to loco regional failure with adjuvant chemotherapy.

Concurrent chemotherapy:

The purpose of simultaneous chemo radiation is to increase loco-regional control and to prevent distant metastasis. The possible synergistic effect has been explained by drugs interface with cell repair after sublethal

or potentially lethal damage or with tumour cell synchronization. Trials show positive results for the strategy of alternating chemotherapy and radiotherapy compared with radiotherapy or chemotherapy alone or neo adjuvant followed by radiotherapy. In additional mucosal toxicity associated with this protocol appears acceptable and similar to that of radiotherapy alone.

Drugs used for chemotherapy:

Methotrexate: The standard palliative drug for recurrent squamous cell carcinoma. Dose is 40mg/m2/week, slowly increased upt 60mg / m2 / week – until toxicity or objective response is achieved.

Bleomycin: Response vary from 6-45% average is 21%. Continuous infusion of bleomycin produces less pulmonary toxicity than bolus injection.

Cisplatin: Most important drug for squamous cell carcinoma of the tongue. 80-100mg/m2 in every 3-4 weeks. Response rate is 28%.

5 Flourouracil: Usually given as IV bolus for 5 days. %FU administrated as infusion instead of bolus was found to have increased

activity, synergistic interaction with cisplatin and enhanced cytotoxicity with modulators like leucovarin.

Taxanes: Paclitaxel and docetaxel binds to the β sub unit of tubulin, induce the formation of stable microtuble bundles and inhibit microtubule depolymerisation. Response rate is 30-40%. Paclitaxel 250 mg / m^2 and 24 hours infusion in every 3 weeks. Docetaxel 100m /m^2 IV bolus in every 3 weeks.

Biologic Therapy for Recurrent Squamous Cell Carcinoma

Patients have moderate to severe depression of cellular and humoral immunity which may be reduced even further by surgery or radiotherapy. Cell lines express high affinity to IL-2 receptors and growth inhibited by IL-2 in vivo and vitro. It has been shown that tumour infiltrating lymphocytes can be increased to 30,000 folds by IL-2. Systemic IL-2 combined with Interferon has anti tumour activity but with substantial toxicity. Research currently focuses on the best way to combine cytokines, retinoids, cytotoxic agents, and radiation therapy.

Principles of Chemoprevention

Chemoprevention is administration of natural or synthetic agents to reverse or suppress carcinogenesis before the development of invasive

cancer. β Carotene or retinol have been extensively studied. Retinoids modulate the growth and differentiation of normal, premalignant and malignant epithelial cells in culture and can suppress cancinogenesis in vivo in various human epithelial tissues. Agents used are selenium and α tocopherol, β carotene, cis retinoids. They are used to treat premalignant lesions like leukoplakia etc but used only in trials.

TREATMENT OF CARCINOMA OF THE TONGUE

Early Disease:

Generally considered that disease control rates for early disease when using either surgery or radiation are equivalent depending on treatment bias. Surgical excision usually entails a hemiglossectomy. Special attention to surgical margins should be exercised. Since disease may spread along the muscle bundles, most T1 lesions can be managed by brachytherapy alone that is Iridium 192 implant. Iridium 192 is inserted via after loading catheters. Catheters are placed in the operating room under general anesthesia. Iridium 192 is loaded for 1-2 days. Localization films are taken and computerised dosimetry is performed. Usually dose is 40-60 cGY per hour range and usual total dose is 6000-7000 cGY.

The patient wears tongue prosthesis during dwell time of the implant to protect the hard and soft palate as much as possible. Because the lesion increases in size when using radiation as primary therapy it is preferred to combine external beam irradiation with implant. First, external beam irradiation can be used as elective neck irradiation simultaneous with tongue. The implant then serves as the boost to the tongue. Secondly, the external beam radiotherapy allows a wider margin of tongue to be treated than does the implant. External RT 5000cGY (200 cGY / day, 5 days a week for 5 weeks). Radiation is certainly suitable for T_1 lesions.

Carcinoma of the tip of the tongue:

Excise this in a 'V' shaped fashion, giving adequate margin so that a new tongue tip can be made.

Carcinoma of the dorsum of the tongue:

Tumour less that 2cm in diameter, excise it in an ellipse and close the tongue primarily. It can also be treated with radiotherapy primarily. Surgical treatment for larger tumours would require an extensive operation and so radiotherapy is preferred. Large tumours cannot be treated by interstitial radiotherapy alone, external beam radiotherapy has to be combined.

Carcinoma of the lateral border of the tongue:

If no glands are palpable then the choice lie between interstitial irradiation and partial glossectomy. If tumour is greater than 3 cm in size then either external beam irradiation is used or hemiglossectomy is performed.

Base of the tongue:

Treatment varies according to different institutions. Some centers advise radiotherapy as a primary modality and surgery for failures. But surgery following radiotherapy improves the survival only by 10%. So initial surgery followed by post operative radiotherapy is recommended to improve the dismal prognosis. Irradiation of Carcinoma of the base of tongue is delivered by parallel opposed external beam portals to the primary site, which also includes the bilateral regional lymph nodes.

Surgical Techniques of Tongue Cancer:

Local Excision of Tongue Cancers:

Many tongue cancers of 1.5cm or less can be managed successfully by local sharp or LASER excision. Excise it with 1cm margin. If the excision

is done by a LASER it is said that grafting of the defect is not needed, otherwise the defect must be repaired with graft.

Hemiglossectomy:

Voice must be considered before going for this operation. If the patient depends on the voice for a livelihood then attempts must be made to leave a good tip of the tongue. Question of standing teeth will also have to be considered. If the patient is to have pre or post operative radiotherapy then all those teeth should be removed before radiation. If primary surgery is being used then only bad teeth are to be removed.

Advanced Carcinoma of the tongue:

Requires mandibulectomy or lingual releasing procedures to gain access to displaced part. The later procedure entails removal of the neck contents prior to primary cancer resection. The tongue is delivered into the neck by releasing musculature attachments posteriorly and mucosal attachments within the oral cavity. Large lesions with mandibular involvement will require composite resection. The term composite resection means removal of the tissue involving multiple anatomically defined structures, one of which includes mandible. Typically it refers to resection of portion of the tongue, floor of the mouth, segment of the mandible.

Treatment Policy for Carcinoma of the tongue:

1. Surgery has no part in the treatment of Sarcoma or Lymphoma. Treatment is based on radiotherapy.

2. T1 and early T2 tumours treated by either surgery or radiotherapy alone. Larger T2 and smaller T3 lesions are best treated by surgery.

3. Massive tumours do very badly with any treatment and best may be treated symptomatically.

4. Radiotherapy of the oral cavity requires that the mandible will be irradiated greater or lesser extend. Osteonecrosis of the mandible is a risk even if no further surgery is performed. But it is an almost certain complication if anything other than wide resection of the mandible is done in any salvage surgery. If mandible has been irradiated, later excision and bone grafting will be impossible.

5. Radiotherapy does not cause dental caries. It does however predispose to periodental disease, which in turn causes marginal caries. Dental extraction before radiotherapy is not mandatory, if future dental care will be regular and thorough. If however the teeth are initially poor and the patient is not dentally conscious, then all the teeth should be extracted and sockets stitched 10 days before radiotherapy.

6. In case of small (T1 or T2) tumour with no palpable neck nodes – the nodes are irradiated in enbloc with primary. Elective irradiation of the lower neck is not necessary. Patient irradiated for large primary with no palpable nodes should receive prophylactic neck irradiation.If, No neck nodes and the primary lesion is treated surgically then the elective Radical neck dissection is performed.

Post treatment Rehabilitation:

No doubt as we see the limitations of current therapeutic strategies to improve on mortality rates for advanced disease, quality of life issues will become increasingly important. Rehabilitation approach begins before the initiation of the treatment – post treatment should begin as early as possible, depending upon the healing and integrity of surgical wounds. Appropriate rehabilitation of tongue begins with choice of reconstruction. Resections contribute sensory loss which impairs initial phase of degultition. The optional reconstruction in most circumstances involves primary closure thereby minimizing large insensate contact surfaces.

Reconstruction:

The principle of reconstruction after glossectomy varies according to the extent of tongue resection. If the residual tongue can be expected to

have sufficient motility such as in patients with hemiglossectomy the oral floor is reconstructed by use of deltopectoral flap, forehead flap, pectoralis major myocutaneous flap or latissmus dorsi myocutaneous flap. The post operative oral function does not vary much with the method of reconstruction. The myocutaneous flap has a great advantage in that, it makes single stage reconstruction possible.

Reconstruction with myocutaneous flap after total and subtotal glossectomy.

It is easy to make the oral floor high and convex by the use of myocutaneous flap. But it is likely to develop secondary atrophy particularly when the muscle is denervated. To prevent secondary drooping of the oral floor.

1. An island flap must be designed about 1 to 1½ times as large as defect of the oral floor. To prevent atrophy of the oral floor – innervation of the muscle must be preserved. It is easier to use latissmus dorsi myocutaneous flap than a pectoralis major myocutaneous flap.

2. The posterior aspect of the oral defect should be extended postero superiorly until it comes up 1/2 to 2/3 of the height of the anterior

glossopalatine arch an island flap should be fixed as high as possible, posteriorly by suturing at least unilaterally.

3. In patients who underwent total glossectomy the transplanted myocutaneous flap can be suspended superiorly and posteriorly by medially transposed bilateral pterygoid muscles connected to each other by a fascia lata graft.

In some patients with T3 tongue cancer it is some times possible to resect the tongue and preserve a portion of its base, some of the muscles of the oral floor and hypoglossal nerve contralaterally. In all these cases secondary drooping of the reconstructed oral floor has been inconspicuous with excellent post operative oral function for speech and deglutition.

Reconstruction with deltopectoral flap after total and subtotal Glossectomy.

An oral floor reconstructed with DP flap is likely to develop secondary atrophy less often than reconstructed with myocutaneous flap. The DP flap must be long enough to reach the middle or posterior axillary line. A simple covering of the oral defect is not sufficient to reconstruct the high oral floor.

To make the reconstructed oral floor high and convex, the broad flap, which is rotated and folded in the oral cavity to allow as much of the flap as possible to be inserted into the oral floor is sutured along the marginal of the oral defects.

MANAGEMENT OF THE NECK NODES

Unilateral neck node under 3 cm (NI)

Surgery is required to control lymph node metastasis in the neck. The standard surgery for dealing with metastatic nodes in the neck is that of Radical neck dissection described by Crile in 1906. Various modifications of neck dissections then came out.

Metastasis in multiple nodes (N2b) or nodes larger than 3cm:

If there is more than one node in a neck and if there is extra capsular spread the prognosis is worsen by 100%. The treatment is radical neck dissection followed by post operative radiotherapy.

Bilateral Neck Nodes: N2c

Staged or simultaneous bilateral neck dissection may be advocated. It is possible to carry out a neck dissection on both sides at same sitting with reasonable safety, although complications are high. One side radical neck dissection and on the other side functional neck dissection can also be done.

Nodes greater than 6cm in size:

If a node is greater than 6 cm it will almost certainly be fixed to adjacent structures and will have exited from the node capsule. If the tumour fixed to jugular vein it is a contraindication for surgery. Fixation to the base of the skull and brachial plexus is almost contraindication for surgery. If it is fixed to overlying skin it is possible to resect the tumour with overlapping skin and reconstruct with myocutaneous flap. When it is fixed to arterial tree, resection of the arterial tree and replaced by venous graft with great operative mortality. As with N2 nodes, since the tumour had exited from the lymph node capsule, it is mandatory to follow any excisional operation with post operative radiotherapy.

No palpable metastasis Node-No:

Pathological involvement of nodes which is clinically not palpable is around 20% in Carcinoma tongue especially in base of tongue tumours. Elective neck dissection has some place in whom unlikely to return for follow up. Elective Radical neck dissection drastically reduces the recurrence rate in the same side of the neck.

TYPES OF NECK DISSECTIONS:

Radical Neck Dissection:

Removal of the entire cervical lymph node group extending from the inferior border of the mandible to clavicle and from the midline up to the anterior border of trapezius. All level of nodes I to VI are included and spinal accessory nerve, internal jugular vein and sternomastoid muscle.

Modified Radical Neck Dissection (MRND)

Excision of all lymph node groups removed by the radical neck dissection with preservation of one or more of the below structures. Spinal accessory, Internal jugular vein, Sternomastoid muscle.

MRND Type I - Preserves spinal accessory nerve.

Type II - Preserves accessory nerve & sternocleidomastoid.

Type III - Preserves accessory nerve & sternocleidomastoid

And Internal Jugular Vein.

Elective Neck Dissection:

Elective neck dissection will be carried in case of No neck nodes, that is prophylactic neck dissection. Surgery on No neck nodes has virtually been abandoned in favour of elective irradiation.

Selective Neck Dissection: This refers to any type of lymph node removal where there is preservation of one or more lymph node groups removed by the radical neck dissection.

1. Supra Omohyoid neck dissection:

Removal of level I, II, III nodes. Posterior limits of dissections are cutaneous branches of the cervical plexus and posterior border of the sternomastoid muscle. Inferior limit is the superior belly of omohyoid muscle where it crosses the internal jugular vein.

Postero lateral neck dissection:

Removal of lymph nodes in levels II, III, IV, V.

Antero lateral Neck dissection:

Removal of II, III, IV level nodes.

Central Compartment neck dissection:

Removal of only level VI nodes.

Extended Radical Neck Dissection:

Removal of one or more additional lymph node groups and / or non lymphhatic structures that are not encompassed by radical neck dissection. This may include parapharyngeal, superior mediastinal, paratracheal lymph nodes. Non-lymphatic structures might include the cartoid artery, the hypoglossal nerve, the vagus nerve and paraspinal muscles.

MATERIALS AND METHODS

Totally 73 patients were chosen from the out patients departments of surgery, surgical oncology, ENT, Radiotherapy and medical oncology from the June 2006 to April 2008. The patients were coming from the entire south Tamil Nadu because, Govt. Rajaji Hospital, Madurai is the highly equipped Teritary centre in South Tamil Nadu. Some of the patients were treated locally at teaching institutions or Govt. hospitals and referred here for further management.

Majority of the patients attended our outpatient departments were in their late stage. In our study roughly 73% of patients were belonging to the stage IV disease and only around 18% were stage I and Stage II. Usually

patients reported for ulcer over the tongue and pain over the ulcer. Usually after the development of pain only, the patients visited the hospitals.

Invariably all the patients were having increased salivation. Patients with Carcinoma of the posterior 1/3 of the tongue usually did not have any symptom at early stage. In posterior 1/3 cancers, the patients visited for pain over the throat or swelling in the neck usually at the later stage and also have dysphagia.

We examined the patients according to the proforma given below. Almost all the patients were with poor oral and dental hygiene. Depending on the stage of the disease, patients were treated with surgery, radiotherapy and chemotherapy.

OBSERVATION AND RESULTS

Roughly 70% of the patients were more than 50 years and only 4.1% of patients were less than 30 years.

65.7% of the patients were smoker. Female patients were not smokers. Usually 10-15 beedies per day for more than 20-30 years. All the patients stopped smoking habits once the symptom of carcinoma tongue developed usually the pain.

Roughly 35% of the patients were tobacco chewer and betal nut chewer. Majority of the patients keep them inside the oral cavity for long time even in the night.

Caries teeth presented in 48% of the patients. Premalignant lesions like leukoplakia were present in around 13% of the patients and submucous fibrosis presented in 3% of the patients. Sharp teeth presented in about 49% of the patients, especially near the site of the ulcer or growth of the tongue. No sharp teeth presented in 51% of the patients. This was due to loss of teeth for treatment purpose, caries teeth and poor dental hygiene.

Male patients especially from the rural area invariably were alcoholics. Alcoholics constituted roughly about 54.7% of the patients.

When we examined the patients, right lateral border of the tongue was the usual site of carcinoma of the tongue. Involvement of right lateral border was 45.2%. Only two patients were having lesions at tip of the tongue. 75% of the patients presented with cervical nodal secondaries. Unilateral involvement of nodes was around 54.5% and bilateral involvement was 41.2% of the patients. Contra lateral nodes were involved in 4.3% of the patients.

FNAC was done in 92% of the nodal positive cases. We did not attempt in very small nodes. The FNAC gave 72.7% positive results for nodal metastasis. Negative in 27.3% of patients. It might be due to nodes per se non metastatic or technically not reached the metastatic sites. So FNAC is the ideal method to find out nodal metastasis.

More than 50% of the patients were subjected to surgical management. 2 patients were having small ulcer cover the tip of the tongue and were treated with excision of the ulcer and primary closure of the defect. Hemiglossectomy done is about 42.6% of the patients. Surgery was done after primary radiotherapy in about 16.7% of the patients.

In the surgical patients block dissection done in 73.4% of the patients. 68.4% of the block dissection were unilateral. Nodes in the block dissection specimen were positive for metastasis in 74.6%.

Radiotherapy given to 68.4% of the patients under study in which 70% of the patients were treated primarily with radiotherapy. Only 30% of the patients received post operative radiotherapy.

Neadjuvant chemotherapy was not given to any patient. Adjuvant chemotherapy along with radiotherapy was given to 16.4% and palliative

chemotherapy given to the massive diseases was 12.3% of the patients. The drugs we used were cisplatin, 5 FU, and Methotrexate.

Recurrence rate in our study was 28.7%. After surgery alone the recurrence was 23.8% and after radiotherapy alone 4.8%. Recurrence was very much minimal with surgery followed by post operative radiotherapy which was 9.5%.

The biopsy report for all the patients came as squamous cell carcinoma. No patient had reconstructive procedure after surgical management of carcinoma of the tongue.

CONCLUSIONS FROM OUR STUDY

In our study the following conclusions were made.

1. It is a male dominated disease.

2. Peak incidence is in the 5^{th} and 6^{th} decades of life.

3. Bad oral hygiene in the form of caries tooth is the commonest etiological factor in non smokers and smoking is the common etiological factors in smokers.

4. Summation effect is noted in carcinogenesis with bad oral hygiene (sharp and caries tooth) and alcoholism.

5. Lateral borders are the commonest area for tongue cancers indicating the dental role in carcinogenesis. In our study right lateral border involvement is more common than left lateral border.

6. Nodal metastasis are quite high in our series indicating the late presentation of the patients and high metastatic capacity of the tongue cancers.

7. FNAC is the most easy, effective and accurate tool to establish the diagnosis of secondary carcinomatous lymphadenopathy (accuracy rate is >90%) with least complications.

8. Surgery for the primary tumour along with operative radiotherapy and block dissection for the secondary node, increases both disease free and overall survival.

9. Surgery is the main modality of treatment of carcinoma of the tongue due to the site involvement of as well as the high incidence of nodal metastasis.

10. Chemotherapy as palliation or adjuvant gives symptomatic relief but does not improve the overall survival.

11. Prognosis of the carcinoma of the tongue directly correlates with AJCC staging at the time of presentation.

12. Recurrence after a single modality of treatment (Radiotherapy) is higher than multimodality of treatment.

13. Though various methods of reconstructions are suggested after surgical resection of tongue, our patients do well in eating and speaking after surgical treatment of tongue cancers without any reconstructive procedures. This indicates the extensive capacity of the tongue for compensatory hyperplasia.

14. Radical glossectomy like subtotal glossectomy achieves better cancer clearance than wedge or partial glossectomy as indicated by increased recurrence rate in conservative surgery.

15. Carcinoma of the tongue is not an uncommon cancer in our area and caries bad prognosis among the oral cancers due to its extensive

lymph nodal metastasis. It is also an agonising cancer in our study because of radiating ear pain, increased salivation, dysphagia etc.

16. Once intrinsic muscle of tongue is involved, the prognosis is bad.

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PROFORMA

A STUDY ON CARCINOMA TONGUE

Name :	Address:	D.O.A:
Age :		D.O.S:
Sex :		D.O.D:

H/O PRESENT ILLNESS

1.	Ulcer / Swelling	-	Site
			Duration
			Onset
			Progress
2.	Pain	-	Onset
			Nature
			Site
			Radiation

			Referred pain over the ear
	Pain during movement	-	On Swallowing - / On protrusion
3.	Salivation	-	Increased / Normal
4.	Movements of tongue	-	Normal / Pain during movements
		-	Deviation on protrusion Right / Left
		-	Inability to move
5.	Voice	-	Normal / Dysarthria / Change in voice
6.	Dysphagia	-	No dysphagia / Pain on swallowing / Inability to swallow
7.	Smell	-	No bad smell / Bad smell / Bad smell to others
8.	Bleeding from the lesion	-	Present / absent
9.	Cough	-	Present / absent
10.	Weight loss	-	Present / absent
11.	Appetite	-	Normal / Loss of appelite
12.	Taste	-	Normal / Altered taste / Loss of taste

H/O PAST ILLNESS

- Hypertensive / Normotensive
- Diabetes / Non diabetes
- Tuberculosis patient/ Non tuberculosis

- Multiple Exposure – present / absent
- Recurrent ulcer in the oral cavity – present / Absent
- Previous swelling in the tongue – Present / Absent
- Oral candidiasis

PERSONAL HISTORY

- Smoker / not a smoker
- Beedi / Cigarette / Cigar / Pipe
- Duration
- Alcoholic / not an alcoholic / duration / amount
- Betel nut chewer
- Tobacco chewer
- Snuff user
- Caries tooth – present / absent
- Syphilis – present / absent
- Dentures

EXAMINATION OF ORAL CAVITY

- Oral hygiene good / poor
- Dental hygiene good / poor
- Dental formula
- Caries tooth present / absent
- Leucoplakia present / absent
- Submucous Fibrosis present / absent
- Candidiasis present / absent

INSPECTION

1.	Ulcer / growth	-	Site – Rt lateral / left / tip / dorsum / ventral surface / post 1/3
		-	Size
		-	Type / Fungating / ulcerating / Fissure/ Nodular / Frozen
		-	Color
		-	Surface
		-	Extension – floor of the mouth / epiglottis / larynx / tonsil / Soft palate / side wall of pharynx
		-	Cross the midline – present / absent
2.	Tongue : Volume	-	Normal / Macroglossia
	Color	-	White / red / blue / black hairy tongue
	Crack / fissure	-	Transverse / Longitudinal

PALPATION

	-	Induration – Present / absent
	-	Bleeding – Present / absent
	-	Sharp tooth – present / absent

NODES	:	Sub mandibular – size / number / mobile / immobile / consistency
Jugulo Diagastric Nodes	:	Size / Number / mobile / immobile / Consistency
Jugulo Omohyoid Nodes	:	Size / Number / mobile / immobile /

		Consistency
Submental Nodes	:	Present / absent
AUSCULATION	:	Creps in lungs – Present / absent
Biopsy	:	Type – wedge / punch / excision
	:	Report – Lab Yes / No
	:	Sq.cell ca / sarcoma / melanoma
FNAC from the nodes	:	Positive / Negative

STAGING: (TNM)

Treatment	:	Surgery
Block Dissection	:	Done / not done
	:	Unilateral / bilateral
	:	nodes – positive / negative
Reconstruction	:	Done / not done
Radiotherapy	:	given / not given
	:	Brachytherapy / external beam
	:	Preoperative / Post operative
Chemotherapy	:	Given / not given
	:	Regimen
	:	Neo Adjuvant / adjuvant / palliative

FOLLOW UP